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# Abstract

**Background:** Perchlorate, thiocyanate and nitrate are sodium/iodide symporter (NIS) inhibitors that block iodide uptake into the thyroid, thus affecting thyroid function. Thyroid dysfunction can adversely affect somatic growth and development in children. To our knowledge, no studies have examined effects of NIS inhibitors on body size measures.

**Objective:** We investigated associations between NIS inhibitors and childhood growth in 940 girls from the Puberty Study of the Breast Cancer and Environment Research Program.

**Methods:** Urine samples collected from girls 6-8 years of age at enrollment (2004-2007) from New York City, greater Cincinnati, Ohio and the Bay Area in California were analyzed for NIS inhibitors and creatinine (C). The longitudinal association between NIS inhibitors and anthropometric measures (height, waist circumference and body mass index (BMI)) during at least 3 visits was examined using mixed effects linear models, adjusted for race and site.

**Results:** Compared to girls in the low exposure group (3.6, 626 µg/gC and 500 mg/gC, median, perchlorate, thiocyanate and nitrate, respectively) girls with the highest NIS inhibitor exposure (9.6, 2343 µg/gC and 955 mg/gC, median perchlorate, thiocyanate and nitrate, respectively) had slower growth in waist circumference and BMI but not height. Significant differences in the predicted mean waist circumference and BMI between the low and high exposure groups were observed beginning at 11 years of age.

**Conclusions:** Higher NIS inhibitor exposure biomarkers were associated with reductions in waist circumference and BMI. These findings underscore the need to assess exposure to NIS inhibitors with respect to their influence on childhood growth.

## Introduction

Disruption of thyroid function is one of the strongest mechanisms linking environmental exposures with adverse health outcomes (Braverman and Utiger 2005). Perchlorate, thiocyanate and nitrate are sodium iodide symporter (NIS) inhibitors that block iodide uptake into the thyroid and thus can affect thyroid function. As known, iodine is necessary for the synthesis of thyroid hormones. Thyroid hormones are essential for normal growth; they promote and modulate the effects of growth hormone secretion (GH)(Burstein et al. 1979) and insulin growth factor (IGF)-1 mediates many of the effects of GH (Miell et al. 1993). These NIS inhibitors are ubiquitous in the environment leading to widespread human exposure, mainly through ingested food and water (Lau et al. 2013; Murray et al. 2008). Perchlorate is a naturally occurring anion that is formed in the atmosphere and is synthesized primarily as ammonium perchlorate for producing solid propellant for rockets, missiles, fireworks, and other explosives. It is also found in some crop fertilizers formerly used in the United States (Mendiratta et al. 1996). Thiocyanate, is found in foods like milk and vegetables (Laurberg et al. 2002) (Michajlovski and Langer 1958). It is also the main metabolite of cyanide exposure coming from tobacco smoke and certain foods like cassava and almonds (Buratti 1997). Nitrates can occur naturally in food, such as green leafy vegetables, or can be added as preservative (in meat and fish).

Ecologic, experimental and observational studies have examined relationships of perchlorate exposure with thyroid hormones in adults, pregnant women, adolescents and infants (Brechner et al. 2000;Chang et al. 2003;Crump et al. 2000;Greer et al. 2002;Li et al. 2000) with mixed results. Associations have been observed between perchlorate and decreased levels of thyroxine ($T_4$) and increased thyroid stimulating hormone (TSH) (Blount 2006; Steinmaus et al. 2007); with the

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strongest associations in women with low iodine and high thiocyanate (Steinmaus et al. 2013).

Associations have also been reported for high nitrate exposure with increased thyroid volume

and thyroid disorders (Aschebrook-Kilfoy et al. 2012; Tajtakova et al. 2006; van Maanen et al.

1994) and increased TSH levels (van Maanen et al. 1994). Perchlorate, thiocyanate and nitrate

exposures are cause for concern given their potential to decrease iodide concentration in the

thyroid). Iodine status may influence growth through its effect on the thyroid (Zimmerman

2007). Data from cross–sectional studies on iodine intake and childhood growth are mixed, most

studies in iodine deficient (ID) areas show retarded height, decreased weight and bone

maturation compared to children in nonendemic areas (Bautista et al. 1982; Azizi et al. 1995;

Thurlow et al. 2006}. Effects of lower level perchlorate exposure have not been well studied in

children including effects on growth. Whether thyroid disruption will occur when iodine is

adequate, and whether these chemical exposures can cause changes in growth is an important

question. In vitro studies of NIS inhibitors indicate that perchlorate, thiocyanate and nitrate act

additively to inhibit iodide uptake (Tonacchera et al. 2004), thus suggesting exposures should be

considered together. We *a priori* hypothesized that the thyroid antagonists perchlorate,

thiocyanate and nitrate would have inverse associations with growth, height, weight, waist

circumference and BMI.

We examined whether exposure to NIS inhibitors measured at one time point were associated

with height, waist circumference and BMI trajectories during childhood in an established cohort

group of young girls with adequate iodine intake.

## Methods

This project was carried out as part of the Breast Cancer and the Environment Research Project (BCERP), a longitudinal study that is investigating early life risk factors for pubertal maturation that may be related to later breast cancer risk. Subjects include 1239 females age (6-8 years) at baseline enrollment (2004-7) with no underlying endocrine medical condition affecting metabolism or growth. The study is conducted at 3 sites: (1) Icahn School of Medicine at Mount Sinai Medical Center (NYC), which recruited only Black or Hispanic girls in East Harlem, New York, with girls seen annually; (2) Cincinnati Children's Hospital/University of Cincinnati (Cincinnati), which recruited in the Cincinnati metropolitan area and through the Breast Cancer Registry of Greater Cincinnati, with girls seen semiannually for the first 5 years and then annually thereafter; and (3) Kaiser Permanente Northern California (KPNC), which recruited KPNC Health Plan members in the San Francisco Bay Area, with girls seen annually. All sites obtained informed consent from parent or guardian and were approved by the institutional review board at each site as well as the Centers for Disease Control {CDC}. Parents or guardians of the participants identified girls' race or ethnicity as black, white, Asian, or Hispanic. Standardized anthropometry and pubertal staging were done at each visit (Biro et al. 2010a). Body size characteristics we looked at were: height, weight and umbilical waist circumference, body mass index (BMI: weight in kilograms divided by squared height in cm). For this analysis we included 940 girls who had anthropometric, dietary and demographic data with at least 3 anthropometric measures over the total of seven years of follow-up (age range 11-16 years at their last follow-up visit). Height was measured to the nearest .1cm, weight to 0.1 kg and waist circumference to 0.1cm. A spot urine sample was collected at baseline for NYC and KPNC and

for Cincinnati, at approximately 6 months after baseline and was used to measure the biomarker analytes.

**Laboratory Analysis**

Perchlorate, thiocyanate, nitrate and iodide concentrations in urine were determined by isotope dilution and ion chromatography/tandem mass spectroscopy (IC/MS/MS) as reported previously (Valentin-Blasini et al. 2007). We measured iodide, which is a form of total iodine. Iodide is an inorganic ion used to measure iodine intake, the micronutrient important for thyroid function. Total iodine methods mathematically convert all forms into a single form and report the sum. Therefore, a total iodine measurement includes iodide and a number of organic forms of iodine. Iodide anion accounts for >90% of total iodine in urine and is the biologically available form that is transported into the thyroid to thyroid hormones (http://www.cdc.gov/nutritionreport/99-02). A total of 940 urines were analyzed (312 from NYC, 247 from Cincinnati and 381 from KPNC). In addition to the internal CDC quality control procedures, we incorporated approximately 10% masked quality control specimens ($n = 89$) from a single urine pool for which the coefficients of variation results were acceptable. Normalization for urine dilution was done by using creatinine-corrected values for perchlorate, thiocyanate and iodide (µg/gC) and for nitrate (mg/gC). We used this method of correcting for urine dilution to be consistent with others examining NIS inhibitors {Blount 2006}. To examine whether results were affected by creatinine adjustment, we analyzed biomarkers uncorrected (µg /l and (mg/L) as well removing extreme creatinine concentrations (<50 mg/dL and >300 mg/dL) (Alessio et al. 1985) and we determined that low creatinine values did not produce extreme biomarker concentrations (data not shown). Results based on creatinine uncorrected values and after excluding samples with extreme values (data not shown) were similar to results from models of creatinine-corrected (reported).

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Additional analyses on a subset of 111 girls from the NYC site were performed to assess the

intraindividual variation in urinary biomarkers over three time points: baseline, one and three

years, usingthree statistical methods described for a previous analysis of variation over 6 months

(Mervish et al. 2012; Teitelbaum et al. 2008). Specifically, we estimated intraclass correlation

coefficient (ICC)(Rosner 2000), Spearman correlation coefficients (SCC), and performed a

surrogate category analysis to assess how well tertile ranking by a single biomarker measurement

represented average concentrations over 3 years (Hauser et al. 2004; Willett 1998).

**Statistical Analyses**

All analyses were conducted using SAS version 9.3 (Cary, NC). Geometric means and

parametric tests of the continuous analyte concentrations were done on natural-log-transformed

values to achieve a near normal distribution. Linear mixed effect models (Proc Mixed in SAS)

were used to evaluate associations of one timepoint perchlorate, thiocyanate and nitrate measures

with repeated outcome anthropometric measurements (height, waist circumference weight, and

BMI) measured during 3-13 visits. This approach allowed random intercepts and took into

account the intrasubject correlation as well as unequal timing of anthropometric measurements.

A quadratic term for age was included in the final model as it improved the fit of the model

assessed by the Akaike information criterion (AIC). Estimates were compared by testing the

difference of the least square means of the fixed effect, exposure group, at each age using the

LSMEANS function in Proc Mixed. Statistical significance was defined as $p<.05$. We compared

the mixed effect model to a Gompertz model, which has been shown to achieve a reasonably

good fit for adolescent human growth (Deming 1957). Results from the Gompertz and mixed

effect model were similar in directionality and effect size (data not shown), which suggests the

mixed effect model adequately described height in our study population.

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Covariates considered as potential confounders were selected on a biologic basis or if they were

related to both growth and urinary biomarker concentrations (chi-square test, T-test, ANOVA

p<.05). Vegetable, dairy and water consumption are considered the major sources of perchlorate,

thiocyanate and nitrate intake in children (Lau et al. 2013; Murray et al. 2008)  and have the

potential to be related to growth. In this study population, vegetable, dairy and water

consumption were associated with concentrations of perchlorate and thiocyanate (and nitrate for

water) but not with any of the growth outcomes and were therefore were not considered

confounders. Additional confounders considered were second hand smoke exposure (no smoker

in the home, smoker in the home, and < or > 35/cigs/week) and age at pubertal development

(defined as breast stage 2 and dichotomized at the median of 9.4 years). To investigate

differences in growth by site, we included an interaction variable for site by age.  Models with

and without this interaction term were similar with respect to the AIC, therefore we present

models without the interaction term for ease of interpretation. Due to the complexity of the

model, variables that did not alter the coefficients for the association between the exposures

categories and the growth outcomes by >15% or improve the fit of the model by a comparison of

the AIC were excluded from the models in a forward selection approach. All final models were

adjusted for site and race/ethnicity (indicator terms for Black, Hispanic, White and Asian).

We analyzed the three NIS inhibitors in combination as categorical variables. In order to

investigate possible combined effects of three thyroid disrupting chemicals we created 3

exposure categories ranked by perchlorate, thiocyanate and nitrate urinary concentrations We

dichotomized at the median perchlorate urinary concentration (5.87μg/gC) urinary thiocyanate

(1180 ug/gC) and urinary nitrate (676 mg/gC) concentrations. The high exposure category

included girls who had all values above the median for all three NIS inhibitors, the low exposure

category included girls with all values below the median, and the medium exposure group included the rest of the girls.

## Results

Our sample included 940 girls with baseline urinary biomarkers (median age: 7.3yrs) and at least 3 (range 3-13) longitudinal anthropometric measures over 7 years of observation. The covariate distributions (urine donation age, race/ethnicity, type of water, vegetable and dairy consumption) in the full cohort (n=1239) and in the subsample included in these analyses (n=940) were similar. Table 1 shows urinary exposure biomarker concentrations corrected for creatinine by selected covariates and overall means compared to 6-9 year old girls included in 2007-8 NHANES surveys (www.cdc.gov/nchs/nhanes.htm). Concentrations of all NIS biomarkers decreased with age of the girl at urine collection. Urine concentrations of perchlorate, thiocyanate, and nitrate differed significantly among the three sites, with the lowest mean values among NYC participants." Perchlorate and nitrate concentrations decreased with increased BMI percentile and all NIS inhibitors increased with >high school education.

It is worth noting that there were no differences in thiocyanate concentrations according to second hand smoke exposure. There were significant differences in perchlorate and nitrate levels by primary drinking water source. Perchlorate and thiocyanate significantly differed by vegetable consumption, whereas dairy consumption was only significantly associated with thiocyanate. There were no significant differences in the analyte concentrations by age of pubertal onset. Concentrations among girls in our study were lower than observed among girls ages 6-9 years in 2007-8 NHANES survey data (www.cdc.gov/nchs/nhanes.htm) (Table 1). Geometric means and

medians of urinary NIS inhibitors by the three combined NIS exposure categories (low, medium

and high) are shown in Table 2.

**Intraindividual Variability**

The covariate distributions (urine donation age, race/ethnicity, BMI, type of water, vegetable and

dairy consumption) in this subsample (n=111) and in the NYC sample used in the main analyses

(n=312) were similar.

However, their caregivers had lower education compared to the full sample (data not shown).

The ICC measure of reproducibility was poor (0.13) for perchlorate, and fair for thiocyanate

(0.24), nitrate (0.35) and iodide (0.25) based on creatinine corrected urine concentrations.

However, when average concentrations over all three samples (used as a surrogate indicator of

their "true" concentrations over time) were categorized into tertiles according to the distribution

of concentrations at each time point, the median value of each tertile increased monotonically

from the lowest to the highest tertile (Supplemental Material, Table S1), thus supporting the use

of a single spot urine sample to classify girls into low, medium, and high exposure categories.

**Growth models**

*Height*

Girls exposed to combined low perchlorate, thiocyanate and nitrate were consistently taller than

the girls with high perchlorate, thiocyanate and nitrate (Table 3). However, differences in height

began to converge by 12 years of age, and heights were similar between the high and low

exposure groups by 13 years of age (Figures 1 and 2).

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### *Waist Circumference and BMI*

Waist circumference and BMI models showed similar patterns, such that after age 7, girls with low exposures had larger values than girls in the medium and high exposure groups, respectively, though differences between the low and high exposure groups were not statistically significant until 11 years of age (Table 3). In addition, differences between the low and high exposure groups increased with age (Figures 1 and 2)..

## Discussion

To our knowledge this is the first study to examine either individual or combined effects of NIS inhibitors on body size and growth during childhood. Combined high exposure to all three NIS inhibitors, (perchlorate, thiocyanate and nitrate urinary concentrations) showed significant differences in growth outcomes at various ages compared to the low exposure to all three NIS inhibitors. Our results are consistent with these chemicals as thyroid antagonists, in that higher exposure to the three NIS inhibitors was associated with smaller mean body size measurements ate each age and slower growth in girls. Beginning at 11 years of age, the predicted difference was significant for mean waist circumference and BMI between the low and high exposure groups. Known sources of exposure and factors associated with growth in children (vegetable, dairy and water consumption) were examined as potential confounders but did not alter associations (data not shown). Chronically impaired iodide uptake is associated with alterations in thyroid hormone levels (Blount et al. 2006; Steinmaus et al. 2007; Steinmaus et al. 2013) . However in our population, iodide levels were generally adequate so that observed associations between exposures and body size measures may be through another mechanism. It is also possible that the various chemicals compete for iodide, but do not necessarily deplete iodide.

Greer et al. suggested that intermittent periods of low iodide intake may not affect thyroid hormone production (Greer et al. 2002).

Chemicals may affect different growth indices during distinct periods of a child's life. Our study examined the prepubertal and pubertal time periods. Early maturing girls have significantly higher BMI and percent body fat than on-time and later-maturing girls (Biro et al. 2010b). When we included the mean age at pubertal development in our models, the association remained the same (data not shown). The trajectories of waist circumference (WC) and BMI are consistent with growth during puberty, as heavier girls grow older, there is also a greater increase in adiposity compared to lighter girls (Biro and Wein. 2010) . WC and BMI have been used as a means of identifying children susceptible at risk for hypertension, type 2 diabetes and cardiovascular disease in both childhood and later as adults (Czernichow et al. 2011b; Freedman et al. 2007). More recently, WC, a measure of visceral fat deposits, and used for defining abdominal obesity is shown to be better than BMI for predicting those conditions in children, including metabolic syndrome and all-cause mortality (Czernichow et al. 2011a; Xi et al. 2014). In this population, WC, BMI and weight are all highly correlated with each other ($r > .90$).

Studies show elevated thyroid hormone levels (TSH, $T_4$ and T3) in obese children and adults compared to normal weight persons (Chomard et al. 1985; Gussekloo et al. 2004; Knudsen et al. 2005; Matzen et al. 1989; Reinehr and Andler 2002; Shalitin et al. 2009). An association between thyroid function and BMI may be due to alterations in energy expenditure or leptin produced by adipocyte tissue, although the mechanism is unclear (Reinehr 2010). Controversy exists as to whether the changes in TSH or other thyroid hormones are causes or consequences of weight status.

Perchlorate associations with thyroid hormone production have been studied in infants and children with mixed results (Brechner et al. 2000; Crump et al. 2000; Lamm 2003; Li et al. 2001; Tellez et al. 2005). Thyroid deficiency is of particular concern during development as these hormones regulate brain development (Haddow et al. 1999). Several studies of NIS inhibitors on thyroid hormones have estimated exposure based on perchlorate levels measured in water supplies. Most have not reported associations with thyroid hormone concentrations on either the pregnant mother or neonate (Amitai et al. 2007; Crump et al. 2000; Li et al. 2001; Tellez et al. 2005), however one study reported elevated TSH levels in newborns whose drinking water supply was perchlorate contaminated compared with those supplied with non-perchlorate contaminated drinking water (Brechner et al. 2000). Several experimental and observational studies using urinary perchlorate biomarkers in adults have reported that perchlorate was not associated with T4 or TSH levels at exposure levels orders of magnitude higher than the median levels found in our study (Braverman et al. 2005;Braverman et al. 2006;Lamm et al. 1999;Lamm 2003). One study found perchlorate negatively associated with T4 only in women with iodine <100 µg/L (Blount et al. 2006), suggesting that iodine levels must be sufficiently low for environmental levels of perchlorate and thiocyanate to overcome compensatory mechanisms that maintain thyroid hormone (Steinmaus et al. 2007) at least in adults.

Previous research on perchlorate and possible thyroid-related health effects has paid little attention to the other common environmental NIS inhibitors, thiocyanate and nitrate. The focus on perchlorate arises in part because the relative potency of it as an NIS inhibitor is 10-200 times that of thiocyanate, and nitrate respectively on a molar basis (Greer et al. 1966; Tonacchera et al. 2004). However, based on average daily intake of percholorate equivalents of nitrates and thiocyanates, a person's exposure to both thiocyanate and nitrate from drinking water and food

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account for a larger proportion of iodine uptake inhibition than does perchlorate exposure (De

Groef et al. 2006). Moreover, in vitro studies of NIS indicate that perchlorate, nitrate, and

thiocyanate act additively to inhibit iodide uptake (Tonacchera et al. 2004).Therefore, it seems

important to study the combination of chemicals.

Nitrate is a natural common chemical contaminant from both food and drinking water intake, and

vegetables account for between 30-80% of the total nitrate intake (Shao-Ting 2007). High levels

of nitrate (>200mg/l) in drinking water have been associated with goiter incidence (Gatseva and

Argirova 2008), increased thyroid volume (van Maanen et al. 1994), and subclinical thyroid

disorders (Tajtakova et al. 2006). A study with lower levels than the above studies and ours,

(mean: 53 mg/l), found no association with thyroid volume (Below et al. 2008). Although nitrate

itself has no toxicity, its metabolites, nitrite and N-nitroso compounds (NOC's), can be toxic. On

the other hand, NOC's, which can be produced in the stomach, have multiple physiological roles,

some of which are positive (Shao-Ting 2007). Thiocyanate has a low toxicity and can be found

as both a metabolite of cyanide, which enters the body mainly from tobacco smoke, and free

thiocyanate, as found in vegetables. The latter form has antibacterial properties (Youso et al.

2012). The fact that nitrates and thiocyanate are capable of both deleterious and beneficial effects

calls for a better understanding of factors associated with their metabolism. Moreover, since

vegetable, dairy and water consumption are major sources of NIS inhibitors (De Groef et al.

2006; Lau et al. 2013; Murray et al. 2008)  the risks and benefits of exposure to NIS inhibitors

need to be carefully considered.

There is increasing evidence linking environmental toxicants to thyroid dysfunction. Studies

have reported associations between thyroid hormone levels and exposure to PCB's (Schell et al.

2008), phthalates (Meeker et al. 2007), perchlorate (NRC 2005), bisphenol A (BPA) (Meeker et al. 2010). Mechanisms underlying thyroid interference by these chemicals are diverse, and include increased inhibition of TH synthesis or increased metabolism of TH's via induction of deiodinases (Zoeller 2007). These same chemicals have also been associated with body size, including phthalates (Hatch et al. 2008; Stahlhut et al. 2007) and BPA (Rubin and Soto 2009), potentially through the thyroid mechanism (Newbold et al. 2008).

A limitation of our study is using one spot urine sample as these chemicals have short half-lives in the body (<1 day except thiocyanate which is about 6 days ) and may not represent one's long term exposure**.** This and an earlier investigation (Mervish et al. 2012) examined repeatability of measures over 3 years and 6 months, respectively. Here, we showed poor-fair agreement (ICC's between 0.13-0.35) of NIS concentrations in samples over 3 years, comparable to the study with a 6 month interval (Mervish et al. 2012). The use of a single spot urine sample would most likely lead to nondifferential misclassification. We also had no information on maternal BMI, birthweight and other maternal indices associated with their offsprings' childhood growth (Laitinen et al. 2001; Terry et al. 2007). An additional limitation is our inability to directly investigate the proposed pathway involving the thyroid because we do not have thyroid hormone measures.

Strengths of this prospective study include longitudinal standardized measures of several parameters of growth. We have at least 3 and as many as 13 anthropometric measurements to examine longitudinal growth. We used mixed effects growth curve modeling which allows examination of timing of differences in growth. We were able to investigate the combined effects

of three thyroid disrupting agents, as animal and laboratory studies have shown that they act in combination to affect thyroid hormone production (De Groef. et al. 2006).

Although growth was associated with exposure to NIS inhibitors in our study, growth is a result of a complex interaction between genetic and environmental factors and not due solely to any one factor. Given the limitations of having one sport urine sample, no thyroid measures and low exposures, these findings need to be further investigated. Nonetheless, changes in growth due to these NIS inhibitors is biologically plausible as normal somatic growth requires the thyroid hormone axis be intact, and alterations in thyroid hormones can potentially affect body size changes (Zimmermann 2007). Studying potential influences of childhood growth is important as childhood growth is predictive of adult disease and mortality (Freedman et al. 2007). However, it is unclear whether the differences in growth associated with exposure in our study population have implications for future growth and health.

# References

Alessio L, Berlin A, Dell'Orto A, Toffoletto F, Ghezzi I. 1985. Reliability of urinary creatinine as a parameter used to adjust values. Int Arch Occup Environ Health 55: 99-106.

Amitai Y, Winston G, Sack J, Wasser J, Lewis M, Blount BC, et al. 2007. Gestational exposure to high perchlorate concentrations in drinking water and neonatal thyroxine levels. Thyroid 17:843-850.

Aschebrook-Kilfoy B, Heltshe SL, Nuckols JR, Sabra MM, Shuldiner AR, Mitchell BD, et al. 2012. Modeled nitrate levels in well water supplies and prevalence of. Environ Health 11:6. doi:10.1186/1476-069X-11-6.:6-11.

Azizi F, Kalani H, Kimiagar M, Ghazi A, Sarshar A, Nafarabadi M, et al. 1995. Physical, neuromotor and intellectual impairment in non-cretinous schoolchildren with iodine deficiency. Int J Vitam Nutr Res 65: 199-205

Bautista A, Barker PA, Dunn JT, Sanchez M, Kaiser DL. 1982. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school age children from an area of endemic goiter. Am J Clin Nutr 35: 127-134.

Below H, Zollner H, Volzke H, Kramer A. 2008. Evaluation of nitrate influence on thyroid volume of adults in a. Int J Hyg Environ Health 211:186-191.

Biro FM, Galvez MP, Greenspan LC, Succop PA, Vangeepuram N, Pinney SM, et al. 2010a. Pubertal assessment method and baseline characteristics in a mixed. Pediatrics 126:e583-e590.

Biro FM, Huang B, Morrison JA, Horn PS, Daniels SR. 2010b. Body mass index and waist-to-height changes during teen years in girls. J Adolesc Health 46:245-250.

Biro FM, Wein M. 2010c. Body mass index and waist-to-height changes during teen years in girls. J Adolesc Health 46:245-250.

Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. 2006. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect 114:1865-1871.

Braverman LE, He X, Pino S, Cross M, Magnani B, Lamm SH, et al. 2005. The effect of perchlorate, thiocyanate, and nitrate on thyroid function in workers exposed to perchlorate long-term. J Clin Endocrinol Metab 90:700-706.

Braverman LE, Pearce EN, He X, Pino S, Seeley M, Beck B, et al. 2006. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. J Clin Endocrinol Metab 91:2721-2724.

Braverman LE, Utiger R. 2005. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. In: Philadelphia, PA:Lippincott Williams & Wilkins, pgs.719.

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Brechner RJ, Parkhurst GD, Humble WO, Brown MB, Herman WH. 2000. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. J Occup Environ Med 42:777-782.

Buratti M. 1997. Validation of urinary thiocyanate as a biomarker of tobacco smoking. Biomarkers 2:81-85.

Burstein PJ, Draznin B, Johnson CJ, Schalch DS. 1979. The effect of hypothyroidism on growth, serum growth hormone, the. Endocrinology 104:1107-1111.

Caudill SP, Schleicher RL, Pirkle JL. 2008. Multi-rule quality control for the age-related eye disease study. Stat Med 27:4094-4106.

Chang S, Crothers C, Lai S, Lamm S. 2003. Pediatric neurobehavioral diseases in Nevada counties with respect to. Birth Defects Res A Clin Mol Teratol 67:886-892.

Chomard P, Vernhes G, Autissier N, Debry G. 1985. Serum concentrations of total T4, T3, reverse T3 and free T4, T3 in moderately obese patients. Hum Nutr Clin Nutr 39:371-378.

Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41.

Crump C, Michaud P, Tellez R, Reyes C, Gonzalez G, Montgomery EL, et al. 2000. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? J Occup Environ Med 42:603-612.

Czernichow S, Kengne AP, Huxley RR, Batty GD, de GB, Grobbee D, et al. 2011a. Comparison of waist-to-hip ratio and other obesity indices as. Eur J Cardiovasc Prev Rehabil 18:312-319.

Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD. 2011b. Body mass index, waist circumference and waist-hip ratio: which is the. Obes Rev 12:680-687.

De Groef B., Decallonne BR, Van der GS, Darras VM, Bouillon R. 2006. Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects. Eur J Endocrinol 155:17-25.

Deming J. 1957. Application of the Gompertz curve to the observed pattern of growth in. Hum Biol 29:83-122.

Freedman DS, Kahn HS, Mei Z, Grummer-Strawn LM, Dietz WH, Srinivasan SR, et al. 2007. Relation of body mass index and waist-to-height ratio to cardiovascular. Am J Clin Nutr 86:33-40.

Gatseva PD, Argirova MD. 2008. High-nitrate levels in drinking water may be a risk factor for thyroid dysfunction in children and pregnant women living in rural Bulgarian. Int J Hyg Environ Health 211:555-559.

Greer MA, Goodman G, Pleus RC, Greer SE. 2002. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect 110:927-937.

Greer MA, Stott AK, Milne KA. 1966. Effects of thiocyanate, perchlorate and other anions on thyroidal iodine metabolism. Endocrinology 79:237-247.

Gussekloo J, van EE, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. 2004. Thyroid status, disability and cognitive function, and survival in old age. JAMA 292:2591-2599.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549-555.

Hatch EE, Nelson JW, Qureshi MM, Weinberg J, Moore LL, Singer M, et al. 2008. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002. Environ Health 7:27.

Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM. 2004. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. Environ Health Perspect 112:1734-1740.

Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, et al. 2005. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90:4019-4024.

Laitinen J, Power C, Jarvelin MR. 2001. Family social class, maternal body mass index, childhood body mass. Am J Clin Nutr 74:287-294.

Lamm SH. 2003. Perchlorate exposure does not explain differences in neonatal thyroid function between Yuma and Flagstaff. J Occup Environ Med 45:1131-1132.

Lamm SH, Braverman LE, Li FX, Richman K, Pino S, Howearth G. 1999. Thyroid health status of ammonium perchlorate workers:a cross-sectional occupational health study. J Occup Environ Med 41:248-260.

Lau FK, deCastro BR, Mills-Herring L, Tao L, Valentin-Blasini L, Alwis KU, et al. 2013. Urinary perchlorate as a measure of dietary and drinking water exposure. J Expo Sci Environ Epidemiol 23:207-214.

Laurberg P, Andersen S, Knudsen N, Ovesen L, Nohr SB, Bulow P, I. 2002. Thiocyanate in food and iodine in milk: from domestic animal feeding to improved understanding of cretinism. Thyroid 12:897-902.

Li FX, Squartsoff L, Lamm SH. 2001. Prevalence of thyroid diseases in Nevada counties with respect to perchlorate in drinking water. J Occup Environ Med 43:630-634.

Li Z, Li FX, Byrd D, Deyhle GM, Sesser DE, Skeels MR, et al. 2000. Neonatal thyroxine level and perchlorate in drinking water. J Occup Environ Med 42:200-205.

Mage DT, Allen RH, Kodali A. 2008. Creatinine corrections for estimating children's and adult's pesticide intake doses in equilibrium with urinary pesticide and creatinine concentrations. J Expo Sci Environ Epidemiol 18:360-368.

Matzen LE, Kvetny J, Pedersen KK. 1989. TSH, thyroid hormones and nuclear-binding of T3 in mononuclear blood cells from obese and non-obese women. Scand J Clin Lab Invest 49:249-253.

Meeker JD, Calafat AM, Hauser R. 2007. Di(2-ethylhexyl) phthalate metabolites may alter thyroid hormone levels in men. Environ Health Perspect 115:1029-1034.

Meeker JD, Calafat AM, Hauser R. 2010. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Technol. 44(4):1458-63.

Mendiratta S, Dotson R, Brooker R. 1996. Perchloric acid and perchlorates.  In: Kirk Othmer Encyclopedia of Chemical Technology.  New York, NY:John  Wiley & Sons, Inc:157-170.

Mervish N, Blount B, Valentin-Blasini L, Brenner B, Galvez MP, Wolff MS, et al. 2012. Temporal variability in urinary concentrations of perchlorate, nitrate, thiocyanate and iodide among children. J Expo Sci Environ Epidemiol 22:212-218.

Michajlovski N, Langer P. 1958. The relation between thiocyanate formation and goitrogenic properties of foods. I. Preformed thiocyanate content of some foods. Z Physiol Chem 312:26-30.

Miell JP, Taylor AM, Zini M, Maheshwari HG, Ross RJ, Valcavi R. 1993. Effects of hypothyroidism and hyperthyroidism on insulin-like growth. J Clin Endocrinol Metab 76:950-955.

Murray CW, Egan SK, Kim H, Beru N, Bolger PM. 2008. US Food and Drug Administration's Total Diet Study:dietary intake of perchlorate and iodine. J Expo Sci Environ Epidemiol 18:571-580.

Newbold RR, Padilla-Banks E, Jefferson WN, Heindel JJ. 2008. Effects of endocrine disruptors on obesity. Int J Androl 31:201-208.

NRC. 2005. Committee to Assess the Health Implications of Perchlorate Ingestion NRC. Health implications of perchlorate ingestion.   Washington, DC:National Academy Press.

Reinehr T. 2010. Obesity and thyroid function. Mol Cell Endocrinol 316:165-171.

Reinehr T, Andler W. 2002. Thyroid hormones before and after weight loss in obesity. Arch Dis Child 87:320-323.

Rosner B. 2000. Fundamentals of Biostatistics, fifth ed. Pacific Grove, CA:Duxbury.

Rubin BS, Soto AM. 2009. Bisphenol A: Perinatal exposure and body weight. Mol Cell Endocrinol 304:55-62.

Schell LM, Gallo MV, Denham M, Ravenscroft J, DeCaprio AP, Carpenter DO. 2008. Relationship of thyroid hormone levels to levels of polychlorinated biphenyls, lead, p,p'- DDE, and other toxicants in Akwesasne Mohawk youth. Environ Health Perspect 116:806-813.

Shalitin S, Yackobovitch-Gavan M, Phillip M. 2009. Prevalence of thyroid dysfunction in obese children and adolescents before and after weight reduction and its relation to other metabolic parameters. Horm Res 71:155-161.

Shao-Ting YX. 2007. Accumulation of Nitrate in Vegetables and Its possible Implications to Human Health. In: 1246-1255.

Stahlhut RW, van WE, Dye TD, Cook S, Swan SH. 2007. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ Health Perspect 115:876-882.

Steinmaus C, Miller MD, Cushing L, Blount BC, Smith AH. 2013. Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08. Environ Res 123:17-24. doi:10.1016/j.envres.2013.01.005. Epub@2013 Mar 7.:17-24.

Steinmaus C, Miller MD, Howd R. 2007. Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 national health and nutrition examination survey. Environ Health Perspect 115:1333-1338.

Tajtakova M, Semanova Z, Tomkova Z, Szokeova E, Majoros J, Radikova Z, et al. 2006. Increased thyroid volume and frequency of thyroid disorders signs in schoolchildren from nitrate polluted area. Chemosphere 62:559-564.

Teitelbaum SL, Britton JA, Calafat AM, Ye X, Silva MJ, Reidy JA, et al. 2008. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. Environ Res 106:257-269.

Tellez TR, Michaud CP, Reyes AC, Blount BC, Van Landingham CB, Crump KS, et al. 2005. Long-term environmental exposure to perchlorate through drinking water. Thyroid 15:963-975.

Terry MB, Wei Y, Esserman D. 2007. Maternal, birth, and early-life influences on adult body size in women. Am J Epidemiol 166:5-13.

Thurlow RA, Winichagoon P, Pongcharoen T, Gowachirapant S, Boonpraderm A, Manger MS, et al. 2006. Risk of zinc, iodine and other micronutrient deficiencies among school age children. Eur J Clin Nutr 60: 623-632.

Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, et al. 2004. Relative potencies and additivity of perchlorate, thiocyanate, nitrate. Thyroid 14:1012-1019.

Valentin-Blasini L, Blount BC, Delinsky A. 2007. Quantification of iodide and sodium-iodide symporter inhibitors in human urine using ion chromatography tandem mass spectrometry. J Chromatogr A 1155:40-46.

van Maanen JM, van DA, Mulder K, de Baets MH, Menheere PC, van der Heide D, et al. 1994. Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid. Toxicol Lett 72:365-374.

Willett W. 1998. Nutritional Epidemiology, second ed. New York, NY:Oxford University Press.

Xi B, Mi J, Zhao M, Zhang T, Jia C, Li J, et al. 2014. Trends in Abdominal Obesity Among US Children and Adolescents. Pediatrics 134:e334-e339.

Youso SL, Rockwood GA, Logue BA. 2012. The analysis of protein-bound thiocyanate in plasma of smokers and nonsmokers as a marker of cyanide exposure. J Anal Toxicol 36:265-269.

Zimmermann MB. 2007. The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood:a review. Thyroid 17:829-835.

Zoeller RT. 2007. Environmental chemicals impacting the thyroid: targets and consequences. Thyroid 17:811-817.

**Table 1: Geometric means (95% CI) of creatinine-corrected urine NIS concentrations according to characteristics at baseline among girls in the BCERP cohort (2004–2007, n = 940).**

| Characteristic | NN | Perchlorate (µg/gC) | Thiocyanate (µg/gC) | Nitrate (mg/gC) | Iodide (µg/gC) |
|---|---|---|---|---|---|
| **Race/Ethnicity** | **N** | | | | |
| Black | 275 | 4.76 (4.37, 5.18) | 1140 (1040, 1260) | 604 (567, 645) | 179 (164, 194) |
| Hispanic | 285 | 5.83 (5.36, 6.33) | 900 ( 820,  989) | 662 (621, 705) | 286 (264, 311) |
| Asian | 53 | 7.12 (5.87, 8.62) | 1610 (1290, 2000) | 931 (803, 1E3) | 260 (215, 314) |
| White | 327 | 7.68 (7.11, 8.30)* | 1410 (1290, 1540)* | 847 (798, 899)* | 243 (225, 262)* |
| **Age at Urine Donation** | | | | | |
| 6-6.99 years old | 290 | 6.44 (5.93, 7.01) | 1150 (1050, 1270) | 726 (680, 774) | 258 (237, 280) |
| 7-7.99 years old | 473 | 6.53 (6.11, 6.97) | 1260 (1170, 1360) | 753 (716, 793) | 237 (222, 253) |
| 8+ years old | 177 | 4.71 (4.23, 5.25)* | 964 ( 853, 1090)* | 610 (562, 663)* | 195 (175, 217)* |
| **BMI Percentile at Urine Donation** | | | | | |
| <50th | 644 | 6.37 (6.02, 6.74) | 1170 (1100, 1250) | 751 (719, 784) | 237 (224, 251) |
| 50-85th | 142 | 6.31 (5.59, 7.12) | 1280 (1110, 1460) | 718 (655, 788) | 234 (208, 264) |
| >85th | 154 | 5.02 (4.47, 5.64)* | 1050 (924, 1200) | 584 534, 638)* | 224 (200, 251) |
| **Caregiver Education** | | | | | |
| <= High school | 272 | 5.16 (4.73, 5.62) | 965 ( 875, 1060) | 648 (606, 694) | 245 (225, 267) |
| > High school | 648 | 6.66 (6.30, 7.05)* | 1260 (1180, 1340)* | 746 (714, 779)* | 233 (220, 246) |
| Not reported | 20 | | | | |
| **Site** | | | | | |
| NYC | 312 | 4.48 (4.14, 4.84) | 742 ( 682,  808) | 572 (538, 607) | 245 (226, 265) |
| Cincinnati | 247 | 6.62 (6.07, 7.23) | 1370 (1240, 1500) | 847 (792, 907) | 207 (189, 227) |
| KPNC | 381 | 7.49 (6.98, 8.04)* | 1520 (1410, 1650)* | 771 (730, 815)* | 245 (228, 264)* |
| **Enviromental Smoking Exposure** | | | | | |
| No Smokers | 695 | 6.40 (6.06, 6.76) | 1160 (1090, 1240) | 739 (709, 771) | 246 (233, 259) |
| >= 1 Smoker, 0 Cigs | 126 | 5.91 (5.20, 6.72) | 1250 (1080, 1440) | 716 (649, 791) | 215 (189, 243) |
| >= 1 Smoker, 1-35 Cigs/week | 48 | 5.23 (4.25, 6.44) | 915 ( 724, 1160) | 561 (478, 658) | 243 (198, 298) |
| >= 1 Smoker, 35+ Cigs/week | 65 | 4.68 (3.91, 5.59)* | 1210  993, 1480) | 589 (514, 676)* | 174 (146, 208)* |
| Not reported | 6 | | | | |
| **Season of Urine Donation** | | | | | |
| Fall | 176 | 5.35 (4.80, 5.96) | 1180 (1040, 1330) | 668 (614, 726) | 213 (191, 238) |
| Spring | 310 | 6.73 (6.20, 7.31) | 1070 ( 975, 1170) | 744 (699, 792) | 246 (227, 267) |
| Winter | 181 | 5.67 (5.10, 6.32) | 1030 ( 917, 1170) | 662 (610, 719) | 234 (211, 260) |
| Summer | 273 | 6.28 (5.75, 6.85)* | 1380 (1260, 1530)* | 754 (705, 807)* | 236 (216, 257) |
| **Primary Drinking Water Source** | | | | | |
| 50/50 Bottle/Spring-Tap | 132 | 6.24 (5.50, 7.07) | 1260 (1100, 1450) | 715 (650, 788) | 227 (201, 257) |
| Primarily Bottle/Spring | 263 | 5.21 (4.77, 5.69) | 1020 ( 926, 1130) | 626 (585, 670) | 222 (203, 243) |
| Primarily Tap | 533 | 6.61 (6.21, 7.04)* | 1210 (1130, 1300)* | 761 (725, 798)* | 244 (229, 260) |
| Not reported | 12 | | | | |
| **Vegetable Consumption Tertiles** | | | | | |
| 1 (0.00-0.741 veg/day) | 288 | 5.38 (4.93, 5.86) | 1040 ( 946, 1150) | 687 (643, 735) | 222 (204, 242) |
| 2 (0.741-1.447 veg/day) | 289 | 6.16 (5.65, 6.72) | 1160 (1050, 1270) | 692 (648, 740) | 257 (236, 280) |
| 3 (1.448-5.18 veg/day) | 289 | 6.83 (6.27, 7.45)* | 1330 (1210, 1470)* | 748 (700, 800) | 232 (213, 252) |
| Not reported | 74 | | | | |

| Characteristic | NN | Perchlorate (µg/gC) | Thiocyanate (µg/gC) | Nitrate (mg/gC) | Iodide (µg/gC) |
|---|---|---|---|---|---|
| **Dairy Consumption Tertiles** | | | | | |
| 1 (0.00-1.576 dairy/day) | 288 | 5.66 (5.18, 6.17) | 995 ( 905, 1090) | 702 (657, 751) | 208 (191, 226) |
| 2 (1.577-2.316 dairy/day) | 289 | 6.25 (5.73, 6.82) | 1170 (1060, 1280) | 717 (671, 766) | 244 (224, 265) |
| 3 (2.317-6.85 dairy/day) | 289 | 6.40 (5.87, 6.98) | 1380 (1260, 1520)* | 707 (662, 756) | 261 (240, 284)* |
| Not reported | 74 | | | | |
| **Age At Breast Stage Two** | | | | | |
| < =9.4 Years Old | 473 | 5.80 (5.43, 6.20) | 1130 (1050, 1220) | 707 (671, 744) | 226 (211, 241) |
| > 9.4 Years Old | 433 | 6.34 (5.91, 6.80) | 1190 (1100, 1280) | 722 (685, 762) | 239 (223, 256) |
| Not Available | 34 | | | | |
| **ALL** | 940 | 6.11 (5.83, 6.41) | 1170 (1110, 1230) | 716 (690, 742) | 234 (224, 245) |
| **NHANES**[a] | 284 | 7.27 (6.56, 8.05) | 1540 (1370, 1730) | 813 (756, 875) | NA |

[a]NHANES 2007-2008, 6-9 year old girls; creatinine corrected geometric mean (www.cdc.gov/nchs/nhanes.html)
*ANOVA $p < 0.05$

**Table 2: Creatinine-corrected urine iodine, and creatinine-corrected urine NIS inhibitor concentrations according to categories of combined NIS exposures (low, medium, and high) in 940 girls (BCERP cohort 2004-2007).**

| Exposure | N | Geo Mean | Med. | Min. | Max. | p95th |
|---|---|---|---|---|---|---|
| **Low perchlorate , thiocyanate and nitrate[a]** | | | | | | |
| Perchlorate (µg/gC) | 196 | 3.26 | 3.59 | 0.51 | 5.86 | 5.5 |
| Thiocyanate (µg/gC) | 196 | 554.61 | 625.84 | 75.77 | 1176.47 | 1103.4 |
| Nitrate (mg/gC) | 196 | 452.35 | 500.1 | 5.92 | 673.12 | 644.1 |
| Iodide (µg/gC) | 196 | 176.74 | 167.7 | 29.23 | 2111.11 | 691.59 |
| **Medium perchlorate , thiocyanate and nitrate** | | | | | | |
| Perchlorate (µg/gC) | 555 | 6.16 | 5.92 | 0.25 | 193.14 | 18.72 |
| Thiocyanate (µg/gC) | 555 | 1179.71 | 1201.72 | 62.34 | 12756.26 | 3709.45 |
| Nitrate (mg/gC) | 555 | 734.83 | 680.25 | 95.74 | 129662.5 | 1895.77 |
| Iodide (µg/gC) | 555 | 235.69 | 230.26 | 28.6 | 4194.92 | 732.05 |
| **High perchlorate , thiocyanate and nitrate[b]** | | | | | | |
| Perchlorate (µg/gC) | 189 | 11.48 | 9.58 | 5.87 | 136.84 | 35.96 |
| Thiocyanate (µg/gC) | 189 | 2438.13 | 2343.28 | 1180.23 | 24807.69 | 5675.68 |
| Nitrate (mg/gC) | 189 | 1066.49 | 955.22 | 676.47 | 6647.73 | 2423.08 |
| Iodide (µg/gC) | 189 | 308.37 | 294.12 | 31.71 | 2636.36 | 1060.22 |

[a]<median concentration of all 3 NIS biomarkers
[b]>median concentration of all 3 NIS biomarkers

**Table 3: Height, waist circumference and BMI by age in low, medium and high combined NIS inhibitor biomarker exposure categories[a]: predicted means and differences (95% CI) based on mixed effects models[b] in 940 girls, BCERP 2004-2007.**

| Age[c] | Low Exposure Category | Medium Exposure Category | High Exposure Category | Difference between Low and High (95% CI) | P value[d] |
|---|---|---|---|---|---|
| **Height (cm)** | | | | | |
| 7 | 121.2 (120.1,122.2) | 120.6 (120.0,121.3) | 120.1 (119.1,121.2) | 1(-0.4,2.5) | 0.172 |
| 8 | 129.0 (127.9,130.0) | 127.8 (127.2,128.5) | 126.9 (125.9,127.9) | 2.1(0.6,3.5) | 0.004 |
| 9 | 136.0 (135.0,137.1) | 134.5 (133.9,135.2) | 133.4 (132.3,134.4) | 2.7(1.3,4.1) | <0.001 |
| 10 | 142.4 (141.3,143.4) | 140.8 (140.1,141.4) | 139.5 (138.5,140.6) | 2.8(1.4,4.3) | <0.001 |
| 11 | 148.0 (146.9,149.0) | 146.5 (145.9,147.2) | 145.4 (144.4,146.4) | 2.6(1.1,4) | <0.001 |
| 12 | 152.8 (151.8,153.9) | 151.8 (151.1,152.5) | 151.0 (150.0,152.0) | 1.8(0.4,3.3) | 0.011 |
| 13 | 157.0 (155.9,158.0) | 156.6 (155.9,157.3) | 156.3 (155.2,157.3) | 0.7(-0.8,2.1) | 0.356 |
| **Waist circumference (cm)** | | | | | |
| 7 | 57.1 (55.5,58.8) | 58.7 (57.7,59.8) | 58.0 (56.4,59.7) | -0.9(-3.2,1.4) | 0.444 |
| 8 | 61.3 (59.7,62.9) | 62.2 (61.2,63.2) | 61.1 (59.5,62.7) | 0.2(-2,2.4) | 0.830 |
| 9 | 65.2 (63.6,66.8) | 65.6 (64.6,66.6) | 64.1 (62.5,65.7) | 1.2(-1,3.3) | 0.295 |
| 10 | 68.8 (67.2,70.4) | 68.8 (67.8,69.8) | 67.0 (65.4,68.5) | 1.9(-0.3,4.1) | 0.091 |
| 11 | 72.1 (70.5,73.8) | 71.9 (70.9,72.9) | 69.7 (68.2,71.3) | 2.4(0.2,4.6) | 0.032 |
| 12 | 75.2 (73.5,76.8) | 74.9 (73.9,75.9) | 72.4 (70.9,74.0) | 2.7(0.5,4.9) | 0.016 |
| 13 | 77.9 (76.2,79.5) | 77.7 (76.7,78.7) | 75.0 (73.4,76.6) | 2.8(0.6,5) | 0.013 |
| **BMI (kg/m$^2$)** | | | | | |
| 7 | 16.3 (15.6,16.9) | 16.7 (16.3,17.1) | 16.4 (15.7,17.0) | -0.1(-1,0.8) | 0.871 |
| 8 | 17.3 (16.6,17.9) | 17.5 (17.1,17.9) | 17.0 (16.4,17.6) | 0.2(-0.6,1.1) | 0.604 |
| 9 | 18.2 (17.6,18.8) | 18.3 (17.9,18.7) | 17.7 (17.1,18.3) | 0.5(-0.4,1.3) | 0.259 |
| 10 | 19.1 (18.5,19.7) | 19.1 (18.7,19.5) | 18.4 (17.8,19.0) | 0.7(-0.1,1.6) | 0.100 |
| 11 | 20.0 (19.4,20.6) | 20.0 (19.6,20.4) | 19.1 (18.5,19.7) | 0.9(0.1,1.8) | 0.038 |
| 12 | 20.9 (20.2,21.5) | 20.8 (20.4,21.2) | 19.8 (19.2,20.4) | 1.1(0.2,1.9) | 0.015 |
| 13 | 21.7 (21.1,22.3) | 21.7 (21.3,22.1) | 20.5 (19.9,21.2) | 1.2(0.3,2) | 0.008 |

[a]Low group is <median concentration of all 3 NIS biomarkers; high group is >median concentration of all 3 NIS biomarkers; medium group includes the all others.
[b] Predicted means and differences were computed from the final model (adjusted for race/ethnicity and site) using the LSMEANS function in Proc Mixed SAS version 9.4.
[c]No estimate was provided for age 6 due to small sample of girls who were exactly 6 years old at enrollment, truncated at age 13.
[d]Significance of the difference between the low and high exposure category.

# Figure Legends

**Figure 1.** Estimated differences (95% CI) in height, waist circumference and BMI, by age between the low and high combined NIS biomarker categories: predicted differences using mixed effects models in 940 girls, BCERP 2004-7. Low group is <median concentration of all 3 NIS biomarkers; high group is >median concentration of all 3 NIS biomarkers. Medium group not shown. Final Mixed effect model was adjusted for race /ethnicity and site. * indicates a p< 0.05 for the predicted differences between the low and high exposure category.

**Figure 2.** Height, waist circumference and BMI growth trajectories by age in the low and high combined NIS inhibitor biomarker exposure categories: predicted means using mixed effects models in 940 girls, BCERP 2004-7. Low group is <median concentration of all 3 NIS biomarkers; high group is >median concentration of all 3 NIS biomarkers. Medium group not shown. Growth curves were derived from the LSMEANS function in SAS 9.4 by each exposure category at each age from the final mixed effect model (adjust for race/ethnicity and site).
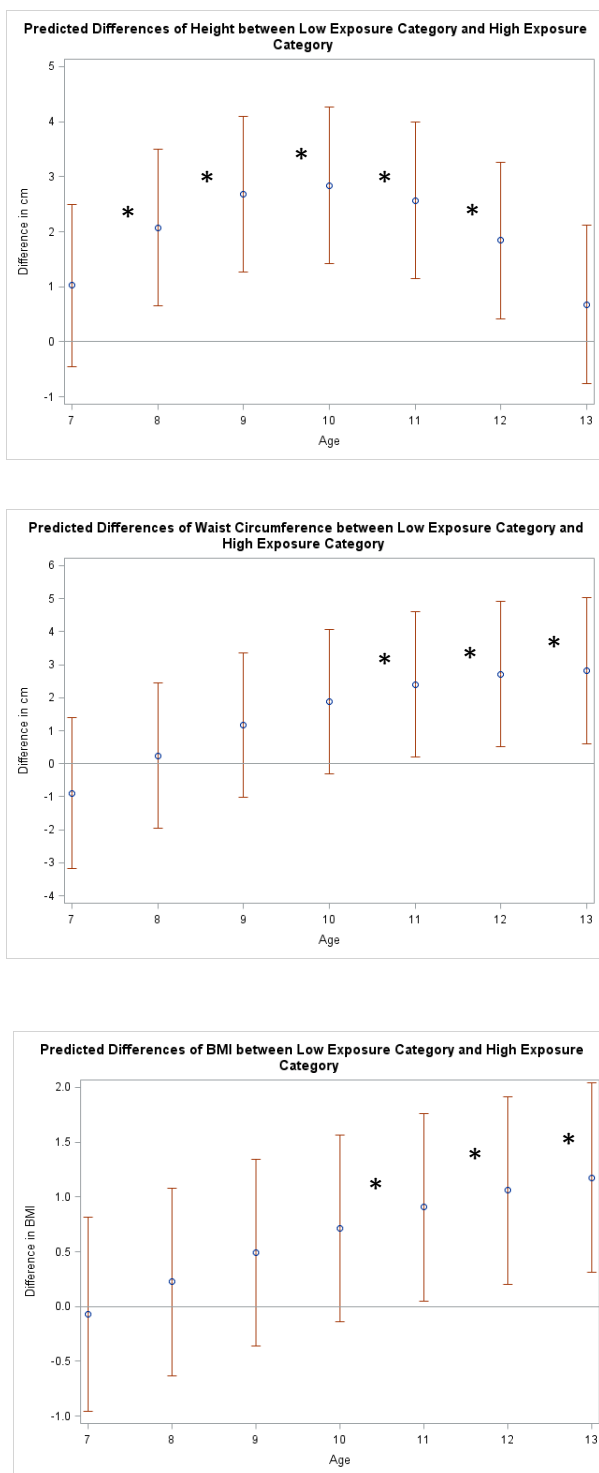
Figure 1.

Figure 2.